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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,328	11/12/2003	Alison Hannah	072121-0366	6441

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,328	HANNAH ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,49-51,53-62 and 64-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,49-51,53-62 and 64-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38, 49-51, 53-62, and 64-66 are presented for examination

Applicants' amendment filed 11/16/2007 has been received and entered into the application. Accordingly, claims 1-6, 9-12, 26-27, 36-38, and 53-55 have been amended, claims 52 and 63 have been cancelled, and claims 65-66 have been added.

Applicants' arguments have been fully considered and are persuasive to overcome the rejections set forth in the previous Office Action. Accordingly, rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application.

In light of the new rejections being applied against the pending claims, this Office Action is **Non-Final**.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 12/18/2007. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Objections

Applicant is advised that should claim 57 be found allowable, claim 65 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an

application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant is advised that should claim 58 be found allowable, claim 66 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, newly added claims 65 and 66 encompass subject matter that is explicitly recited in claims 57 and 58. Specifically, claims 57 and 58 recite administration of the same compounds recited in claims 65 and 66. It is noted that claims 57, 58, 65, and 66 all depend from claim 53.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-55 and 64 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims administration of one or more compounds having three different formula (i.e., compounds **1-3** as disclosed at page 5 and pages 51-53 of the

specification) or "an active metabolite thereof" (*e.g.*, claim 53). There is insufficient written description of active metabolites of the claimed compounds, other than the two specific metabolites recited in the claims and disclosed in the specification (*e.g.*, the N-oxide metabolite of compound **1**, *i.e.*, compound **2**, and the N-desmethyl metabolite of compound **1**, *i.e.*, compound **3**). See Example 6 at pages 51-53. The lack of written description of the instantly claimed active metabolites is further compounded by the fact that the metabolites as instantly claimed must not only be metabolites of the recited compounds, but must also be "active". Accordingly, other than the two specific metabolites of compound **1**, Applicants have not demonstrated possession of the claimed active metabolites of compounds **1-3** as recited in claim 53.

Although general techniques such as cellular assays may be known in the art, this fact fails to diminish the amount of experimentation that the skilled artisan would have to undertake to identify, let alone determine the full scope of, the claimed active metabolites as recited in claim 53, particularly in view of the fact that this genus as a whole is not one that is well-known or well-defined in the art such that the skilled artisan would readily envision those compounds that are within the scope of the claimed genus.

The need for testing amongst varying species of compounds to determine the full scope of the genus of compounds encompassed by "active metabolite thereof" as instantly claimed demonstrates that Applicants were not in possession of the full scope of the genus now presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by

disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163.

Despite the disclosure of the specific compounds defined in, *e.g.*, claim 53, two of which are metabolites of compound **1**, it remains that the specification provides non-limiting exemplification of a solely functional genus of agents that may be used within the context of the present invention. With the exception of compounds **2** and **3** as defined in the original disclosure and claims, Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other agents that are active metabolites of the claimed compounds, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify other agents that may be amenable for use in the present invention, it remains that at the time of the invention, Applicants had not identified such compounds, and, therefore, did not have written description of the full scope of the genus claimed.

Claims 1-38, 49-51, 53-62, and 64-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cancers wherein the cancer cells express receptor tyrosine kinases selected from FLT-1, VEGFR2, VEGF3, FGFR3, FGFR1, c-kit, and/or FLT-3, does not reasonably provide enablement for treating cancers wherein the cancer cells express other receptor tyrosine kinases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention, state and predictability of the art, and relative skill of those in the art</u>

The invention relates to the general treatment of cancer, wherein the cancer cells express "a receptor tyrosine kinase".

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be an oncologist with several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

The treatment of cancer is highly unpredictable due to differing forms of cancerous cells, their location, their potential for metastases, the fact that cancer therapeutics are palliative rather than curative, and that cancer treatment readily harms normal tissues. It is further noted that there are no known anticancer that are therapeutically effective against all cancers. While Applicants' claimed invention relates to the treatment of cancers "expressing a receptor tyrosine kinase", the pathology of cancer is generally unpredictable and inhibition of a single enzyme is not generally accepted in the art as being predictable of clinical efficacy.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 1) vary broadly, reciting the treatment of cancer wherein the cancer cells express "a receptor tyrosine kinase". Others, such as claims 59-62 and 64, are narrower, reciting specific receptor tyrosine kinases. However, it is noted that their is no evidence of record that the claimed compound is an inhibitor of Tie-2, Fyn, Lck, or c-Abl as recited in claims 59-62 and 64.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides numerous *in vitro* assays for assaying the activity of the claimed compounds in inhibiting receptor tyrosine kinases (Example 3, pages 41-44). While it is disclosed that compounds 1-3 were tested for inhibition of FLT-1, VEGFR2, VEGFR3, FGFR3, Tie-2, and FGFR1 kinases (page 42, [0092]), it is only stated that each of these compounds displayed IC_{50} values of less than 10 μM for FLT-1, VEGFR2, VEGFR3, and FGFR1. There is no evidence of activity of the compounds for inhibition of Tie-2. Similarly, while assays are disclosed for inhibition of Fyn, Lck, and c-Abl (pages 42-43, [0093]-[0094]), no data is presented demonstrating that the compounds inhibited these receptor tyrosine kinases. While there is evidence that compound **1** inhibits the proliferation of a number of different cancer cell lines (Table 1), there is little guidance with respect to which cancers express which receptor tyrosine kinases and thus would be more amiable to treatment with the claimed compounds.

The mechanism of action of a therapeutic agent is no doubt important, however, inhibition of a enzyme in an *in vitro* system cannot be said to reasonably correlate to clinical activity. This is especially true when the claims, such as here, encompass the treatment of cancer wherein the cancer cells express any receptor tyrosine kinase. Further, it is noted that Applicants do not provide any guidance with respect to determining whether a particular cancer patient has cancer cells expressing a receptor tyrosine kinase.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed compounds could be predictably used as a treatment for all cancers wherein the cancer cells express any receptor tyrosine kinase as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because the instantly claimed compounds inhibit FLT-1, VEGFR2, VEGF3, FGFR3, FGFR1, c-kit, and/or FLT-3 tyrosine kinases *in vitro* they must therefore, *a priori*, be useful in the treatment of cancers whose cells express any receptor tyrosine kinase. However, only compound **1** has been shown to inhibit

cancer cell proliferation *in vitro* and tumor growth *in vivo* (Examples 1 and 4) and it is unclear what receptor tyrosine kinases (if any) are expressed in the cancer cell lines tested. Further, there is no evidence of record that the disclosed metabolites of compound **1** (compounds **2** and **3**) as recited in claim 53 and claims dependent from claim 53 have any activity in inhibiting cancer cell proliferation or tumor growth of cancer cells expressing a receptor tyrosine kinase.

Determining if any particular claimed compound would treat any particular cancer expressing any particular receptor tyrosine kinase would require formulation of the compound into a suitable dosage form and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the guidance and direction provided by Applicants.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

February 1, 2008

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER